REMARKS/ARGUMENTS

In response to the Non-Final Rejection mailed May 9, 2003, Applicants have amended claims 85 and 86 and present the following remarks.

Claim 85 has been objected to as containing various typographical errors and abbreviations. They have been corrected. Accordingly, this objection should be withdrawn.

Claims 85-94 and 96-97 were rejected under 35 USC 112, second paragraph as being unclear in the term "a degree of efficacy" of an agent because the term "efficacy" is not specifically defined or its "degree" is undefined and apparently not understood by the examiner.

The terms "efficacy" as well as "toxicity" (which is apparently clear to the examiner) are both relative terms and frequently dose dependant. Note that all of the claims require a step of "comparing ... to a control sample or other sample exposed to a known toxic or a known effective agent to determine ... toxicity or an effective response". Thus, the term "degree of efficacy" as used in the claims is determined by the results from a comparison. The examiner contends that the term is unclear absent a statement of what effect is referred to. Again, if one is comparing to the efficacy of a "known effective agent" then one is clearly comparing to the same effect as that of the "known effective agent". To compare to a known effective agent, one is inherently choosing to compare for a "known" effect. It is true that drugs sometimes have multiple effects and even unknown effects because the effects, side effects and toxicities of most drugs are not completely known. However, applicants assert that the amount of alteration in the amounts of certain specific proteins (one or more of those claimed) does correlate to the "efficacy" of the agent when compared to a positive and/or negative control.

The specification emphasizes the nature of efficacy is determined by comparison in many locations, three of which are on page 6, lines 3-6 (underlining added):

"It is yet another further object of the present invention to compare protein markers of candidate drugs to protein markers for known antilipemic agents to determine comparative efficacy, toxicity and whether similar mechanisms of action are involved."

Also page 23, lines 24-29 (underlining added):

"The degree of its induction thus may reflect the pharmacological potency of an HMG-CoA reductase inhibitor to inhibit HMG-CoA reductase and hence serves as a marker to compare efficacy among members of the statin family of compounds and between families of chemically unrelated agents with a similar mode of action."

Also, the paragraph bridging pages 62-63 provides a discussion:

"The proteins in the biological sample from an agent treated organism or tissue may be tested against a number of other groups depending on the data desired. The simplest comparison is to untreated controls. However, comparisons to positive and negative treated controls may also be performed. In that situation, the positive controls include samples from treatments with an agent having the same mechanism of action and agents having a different mechanism but the same general effect. Negative treated controls may be from samples treated with an agent with the same mechanism of action but having an opposite effect or samples treated with agents having an unrelated mechanism. To best determine which agents have an unrelated mechanism, it is desirable to compare to a composite effect of many drugs and other agents, preferably from a pharmaceutical proteomics large database. The comparison to the positive control same mechanism of action and the negative control same mechanism of action may be seen as agonist/antagonist effects and correlations between these two control groups provides a further source for protein markers."

The examiner has asserted that the claims are too broad and one would not know what is included or excluded from the claim. Not so. One skilled in the art will know how they obtained a sample. One of skill in the art will know if they are measuring a specific protein. One skilled in the art will know if they are comparing the measured amount to the amount in a control or a previously differently treated sample. These are clear physical steps and simple data analysis. Therefore, regardless of the claim scope, the claims are definite and clear to those skilled in the art.

Claim 96 has also been rejected because the terms "effective amount" and "greater than effective amount" are not clearly defined. While applicants consider these terms to be

clear, the claim was amended to use the same terminology as the specification, i.e. "dosage" instead of "amount". Examples are found on page 16, lines 10-14:

"For example, the dosage employed would be sufficient to alter the protein markers' abundance to approximately the same extent as the alteration to the same marker caused by one or more known antilipemic pharmaceuticals such as those listed in the examples below."

Also, note page 70 lines 8-12 :

"A quick method for reading this is to compare the ratios to the controls. This is believed to be due to different modes of action of these two drugs. Combinations of pharmaceutical compounds in a composition may be prepared using known effective dosages of these known pharmaceuticals in their conventional dosages."

Claim 86 has been rejected as broader than the scope of the base claim. This claim has been amended to remove the proteins not included in the base claim.

Claims 85-94, 96 and 97 were rejected under 35 USC 112, first paragraph, for similar reasons as given in the second paragraph rejection above. The examiner contends the disclosure does not describe "a degree of toxicity and/or efficacy" and "quantifying a degree". The examiner acknowledges the disclosure is enabling for visualizing the changes but not for a quantitative assay of toxicity/efficacy. The rejection is respectfully traversed.

The protein concentration measurements made in the specification are quantitative for both the test sample and the controls. During the data analysis, a comparison is made between the test sample and the known agent treated sample. By comparing the change in a protein's abundance in a test sample compared to the change in the same protein's abundance in a known agent treated sample, one can readily determine which change made is greater or less than each other. Depending on which protein one chooses to measure, the relative change may correlate to relative efficacy and relative toxicity.

A quantitative measurement relative to a standard is a quantitative measurement. Contrary to the examiner's assertion, this does indicate a degree of toxicity or efficacy because one already knows the degree of toxicity or efficacy of the standard. In the

specification examples, the standards are all FDA approved drugs, which were extensively studied and have well-established toxicity and efficacy characteristics and are the standards by which a candidate agent is compared.

The examiner elaborates by urging that a calibration curve is not taught. This is not correct. For example, in Table 2 of the specification, many examples are readily seen by simple scanning. Below are some examples from the first three proteins and the last three proteins in Table 2:

	Control	Low Dose	High Dose
MSN	AVOL	AVOL	AVOL
73	19379	18113	16433
101	13120	10860	9189
106	7287	6522	2822

The last three on table 2 are:

	Control	Low Dose	High Dose
MSN	AVOL	AVOL	AVOL
229	15082	13725	10693
413	4951	6944	14671
1250	547	672	2238

While the proportional change with changing pharmaceutical dosage does differ from protein to protein, one can still see that a calibration curve can be drawn. For example control rat liver, low dose of Lorelco treated rat liver and high dose of Lorelco treated rat liver, have a measured amount of protein MSN 73 (the first line of data in Table 2). With increasing concentration of the drug, this particular protein decreases. Likewise, similar samples with control, low dose Pravachol and high dose Pravachol have a measured amount of protein MSN 1250, which increases with an increased concentration of that drug. Accordingly, the specification does show a quantitative assay toxicity/efficacy relative to negative controls and different dosages of positive controls of a known effective drug.

The examiner has criticized the specification indicating that protein changes are not correlated to level of cholesterol in the blood of humans being treated with the drug. While specific data is not shown, the drugs used were approved by the FDA as cholesterol and other blood lipid lowering drugs. The effects in humans of these commercially sold drugs are well known to those skilled in the art. Therefore, applicants do not need to demonstrate that the drugs actually reduce cholesterol etc. and merely need to show that certain proteins are altered when exposed to therapeutic or toxic dosages of the known drugs.

In the paragraph bridging pages 5 and 6 of the rejection mailed May 9, 2003, the examiner correctly notes that different proteins may change or not change in an unpredictable manner. The examiner urges that undue experimentation is needed to make such a determination. While this statement was true before experiments performed by the inventors, the inventors have undertaken the undue experimentation and determined the surprising results. Experimentation was done and it was determined which proteins respond to agents with amounts of certain proteins that actually change in a statistically significant manner between test and control samples. These are the proteins that are recited in the claims.

The examiner has also contended that the claims do not recite the measurement of toxicity and efficacy as determined a low and high doses of a drug. Actually claim 85 does claim comparing the levels of said markers to the levels of the same markers in a control sample known effective and known toxic samples in the last paragraph. Claim 85 does recite that the data is used to determine the relative amount of toxicity or efficacy based on the relative amount of proteins, which increase or decrease in abundance compared to the standards.

The examiner also notes that the claims lack any recitation of testing plural dosages of the test agent. This is true for the claim, the specification teaches much more, namely the use of many dosages of the test agent compared to different dosages of a standard. The specification provides and adequate enabling disclosure and the claim clearly sets forth the limits of the enabled invention. Accordingly, the specification and claims meet the standards of 35 USC 112, first paragraph and the rejection should be withdrawn.

Claims 85-94, 96 and 97 were rejected under 35 USC 103 as unpatentable over Anderson et al (1991) in view of Anderson et al (1995) and Anderson et al (1996). The examiner urges that Anderson 1991 discloses a similar experiment and measured several of the claimed proteins. Anderson 1995 is cited to show identification names for previously MSN. The examiner notes that Anderson 1996 performs a similar experiment using a range of doses for a drug and again measures several of the claimed proteins.

Regardless of what general method the combination of references may or may not make, the presently claimed list of proteins in claims 85+ are not taught to be altered in any of the references.

The examiner has pointed to actin gamma, apo A-I lipoprotein, HMG-CoA and catalase as being listed in Table 1 and 2 of Anderson 1991. However, Anderson 1991 does not state that actin gamma was altered in abundance between the control and the test sample. Indeed, the list of proteins, which did change in abundance from drug exposure, does not exclude actin gamma. This is a direct teaching away from the present invention. Anderson 1991 measured actin gamma and found no change in its abundance. Therefore, it would NOT be obvious to measure actin gamma looking for a change in its abundance.

Likewise, apolipoprotein A-I, and catalase were measured by Anderson 1991 but found to not change in abundance with drug treatment. One would certainly not be motivated to measure the abundance of these after the prior art stated that they did not change in abundance. As for HMG-CoA, Anderson 1991 measures cysolic HMG-CoA synthetase (MSN 413) not the claimed HMG-CoA synthase, mitochondrial frag. (EC 4.1.3.5) which is MSN 361 according to Table 3 of the specification. The cytosolic and the mitochondrial fragment are actually different proteins with different sequences even though they have a similar enzyme activity. The cytosolic and the mitochondrial fragment form different spots on a 2-D gel of a rat liver as shown by having different Master Spot Numbers. According to Anderson 1991, table 1 MSN 413 has a molecular weight of about 53,700 and MSN 361 has a molecular weight of about 40,100. Also, according to Anderson 1991 table 2, cytosolic HMG-CoA synthetase 413 was determined by antibody binding. This same antibody apparently cross-reacted with MSNs 133, 144 and 235. There is no mention of the antibody cross-reacting with MSN 361, which further indicates that the two

proteins are different. Therefore, even though cysolic HMG-CoA synthetase (MSN 413) and HMG-CoA synthase, mitochondrial frag. (EC 4.1.3.5) (MSN 361) have a very similar name, they appear to represent different proteins.

The examiner also noted that Anderson 1996 shows quantitative changes in cytosolic epoxide hydrolase, 80 kDa bifunctional enzyme and unidentified spot IEF 163. Applicants have canceled epoxide hydrolase from the claims and thus this issue is moot. As for 80 kDa peroxisomal bifunctional enzyme and spot IEF 163, these also do not appear to be in the list of claimed proteins.

The examiner has stated that one would expect some proteins to change in abundance in a tissue in response to chemical exposure. That may be true but the claims do not recite any protein, only certain ones which were not previously shown to change in abundance and in the prior art apparently did not change at all.

Therefore, even if one were to agree with the assertions made in the rejection, the references still do not suggest any of the proteins listed in the Markush group of claim 85 would be changed in abundance when exposed to an agent. It even appears that some or all of the proteins recited in claims 85+ were at some point measured by the prior art 2-D electrophoresis and no changes were noted in abundance of any of these proteins between the control samples and the test samples. Therefore, it would not be obvious to measure these proteins without some indication that a change in their abundance is expected or meaningful. Accordingly, the rejection under 35 USC 103 has been overcome and should be withdrawn.

In view of the above amendments and comments, the claims are now in conditions for allowance and applicants request a timely Notice of Allowance be issued in this application.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,

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